DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

TRANSMITTED BY FACSIMILE

Mihael H. Polymeropoulos, M.D.
President and Chief Executive Officer
Vanda Pharmaceuticals Inc.
2200 Pennsylvania Ave NW, Suite 300E
Washington, DC 20037

RE: NDA 022192
FANAPT® (iloperidone) tablets, for oral use
MA 539

NDA 205677
HETLIOZ® (tasimelteon) capsules, for oral use
MA 137

WARNING LETTER

Dear Dr. Polymeropoulos:

The Office of Prescription Drug Promotion (OPDP) of the U.S. Food and Drug Administration (FDA) has reviewed the Vanda Pharmaceutical's (Vanda) webpage[1] titled, "Products" for FANAPT® (iloperidone) tablets, for oral use (Fanapt), and HETLIOZ® (tasimelteon) capsules, for oral use (Hetlioz). This webpage is false or misleading in that it presents information about the benefits of Fanapt and Hetlioz, but fails to include **any** risk information about either drug. Thus, the webpage misbrands Fanapt and Hetlioz within the meaning of the Federal Food, Drug and Cosmetic Act (FD&C Act) and makes their distribution violative. 21 U.S.C. 352(a) & (n); 321(n), 331(a). *See* 21 CFR 202.1(e)(5). This violation is concerning from a public health perspective because it creates a misleading impression about the safety of Fanapt and Hetlioz. Of particular concern is that Fanapt is a drug that bears a Boxed Warning due to serious, life-threatening risks, including increased mortality in elderly patients with dementia-related psychosis, as well as numerous other warnings.

Background

Below are the indication and summary of the most serious and most common risks associated with the use of Fanapt and Hetlioz.[2]

[1] Available at http://www.vandapharma.com/products.html (Last Accessed October 18, 2018).
[2] This information is for background purposes only and does not necessarily represent the risk information that should be included in the promotional piece cited in this letter.

According to the FDA-approved product labeling (PI):

> FANAPT® is indicated for the treatment of schizophrenia in adults.
>
> When deciding among the alternative treatments available for this condition, the prescriber should consider the finding that FANAPT is associated with prolongation of the QTc interval . . . . Prolongation of the QTc interval is associated in some other drugs with the ability to cause torsade de pointes-type arrhythmia, a potentially fatal polymorphic ventricular tachycardia which can result in sudden death. In many cases this would lead to the conclusion that other drugs should be tried first. Whether FANAPT will cause torsade de pointes or increase the rate of sudden death is not yet known.
>
> Patients must be titrated to an effective dose of FANAPT. Thus, control of symptoms may be delayed during the first 1 to 2 weeks of treatment compared to some other antipsychotic drugs that do not require a similar titration. Prescribers should be mindful of this delay when selecting an antipsychotic drug for the treatment of schizophrenia.

Fanapt is contraindicated in patients with known hypersensitivity to Fanapt or to any components in the formulation. The PI for Fanapt contains a Boxed Warning regarding increased mortality in elderly patients with dementia-related psychosis. In addition, the WARNINGS AND PRECAUTIONS section includes risk information regarding: cerebrovascular adverse reactions, including stroke, in elderly patients with dementia-related psychosis; QT prolongation; neuroleptic malignant syndrome; tardive dyskinesia; metabolic changes; seizures; orthostatic hypotension and syncope; falls; leukopenia, neutropenia and agranulocytosis; hyperprolactinemia; body temperature regulation; dysphagia; suicide; priapism; and potential for cognitive and motor impairment. The most common adverse reactions associated with Fanapt are dizziness, dry mouth, fatigue, nasal congestion, orthostatic hypotension, somnolence, tachycardia, and weight increased.

According to the PI, Hetlioz is indicated for the treatment of Non-24-Hour Sleep-Wake Disorder (Non-24). The WARNINGS AND PRECAUTIONS section includes risk information regarding somnolence. The most common adverse reactions associated with Hetlioz are headache, increased alanine aminotransferase, nightmares or unusual dreams, and upper respiratory or urinary tract infection.

False or Misleading Risk Presentation

Promotional materials misbrand a drug if they are false or misleading with respect to risk. The determination of whether promotional materials are misleading includes, among other things, not only representations made or suggested in promotional materials, but also failure to reveal facts material in light of the representations made or with respect to consequences that may result from the use of the drug as recommended or suggested in the materials.

The webpage includes claims and/or representations about the uses and/or benefits of Fanapt and Hetlioz; however, it fails to communicate **any** risk information about the products. We acknowledge that the webpage includes the statements, “For U.S. full prescribing

information, including box warnings and safety information, please visit www.fanapt.com," and "Full HETLIOZ® Prescribing Information can be found at: www.hetlioz.com." However, this does not mitigate the omission of risk information from the webpage. By omitting the risks associated with Fanapt and Hetlioz, the webpage fails to provide material information about the consequences that may result from the use of the drugs and creates a misleading impression about the drugs' safety. This misleading presentation is especially problematic from a public health perspective due to the serious and potentially life-threatening risks associated with the drugs, such as those contained in Fanapt's Boxed Warning.

Conclusion and Requested Action

For the reasons discussed above, the webpage misbrands Fanapt and Hetlioz within the meaning of the FD&C Act and makes its distribution violative. 21 U.S.C. 352(a) & (n); 321(n), 331(a). *See* 21 CFR 202.1(e)(5).

OPDP requests that Vanda immediately cease misbranding Fanapt and Hetlioz and/or cease introducing the misbranded drugs into interstate commerce. Please submit a written response to this letter on or before November 5, 2018, stating whether you intend to comply with this request, listing all promotional materials (with the 2253 submission date) for Fanapt and Hetlioz that contain representations such as those described above, and explaining your plan for discontinuing use of such materials, or, in the alternative, for ceasing distribution of Fanapt and Hetlioz. Because the violation described above is serious, we request, further, that your submission include a comprehensive plan of action to disseminate truthful, non-misleading, and complete corrective messages about the issues discussed in this letter to the audience(s) that received the violative promotional materials. In order to clearly identify the violative promotional piece(s) and/or activity and focus on the corrective message(s), OPDP recommends that corrective piece(s) include a description of the violative promotional piece(s) and/or activity, include a summary of the violative message(s), provide information to correct each of the violative message(s), and be free of promotional claims and presentations. To the extent possible, corrective messaging should be distributed using the same media, and generally for the same duration of time and with the same frequency that the violative promotional material was disseminated.

Please direct your response to the undersigned at the **Food and Drug Administration, Center for Drug Evaluation and Research, Office of Prescription Drug Promotion, 5901-B Ammendale Road, Beltsville, Maryland 20705-1266**. A courtesy copy can be sent by facsimile to (301) 847-8444. To ensure timely delivery of your submissions, please use the full address above and include a prominent directional notation (e.g. a sticker) to indicate that the submission is intended for OPDP. Please refer to MA 539 and MA 137 in addition to the NDA numbers in all future correspondence relating to this particular matter. All correspondence should include a subject line that clearly identifies the submission as a Response to Warning Letter. OPDP reminds you that only written communications are considered official.

The violations discussed in this letter do not necessarily constitute an exhaustive list. It is your responsibility to ensure that your promotional materials for Fanapt and Hetlioz comply with each applicable requirement of the FD&C Act and FDA implementing regulations. If you

believe that your products are not in violation of the FD&C Act, include your reasoning and any supporting information for our consideration.

Failure to correct the violations discussed above may result in FDA regulatory action, including seizure or injunction, without further notice.

Sincerely,

{See appended electronic signature page}

Andrew S.T. Haffer, Pharm.D.
Division Director
Division of Advertising & Promotion Review 1
Office of Prescription Drug Promotion

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

ANDREW S HAFFER
10/22/2018